| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| L1 | 18 | Ruvkun NEAR Gary | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2005/07/11 08:55 |
| L2 | 39 | DAF-16 | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2005/07/11 08:55 |
| L3 | 7323 | ELEGANS | US-PGPUB; USPAT; EPO; JPO; DERWENT | OR | ON | 2005/07/11 08:56 |
| L4 | 538 | AFx fkhr | US-PGPUB; USPAT; EPO; DERWENT | OR | ON | 2005/07/11 08:56 |
| L5 | 14 | L2 and L3 and L4 | US-PGPUB; USPAT; EPO; DERWENT | OR | ON | 2005/07/11 08:56 |
| L6 | 65867 | insulin | US-PGPUB; USPAT; EPO; DERWENT | OR | ON | 2005/07/11 08:56 |
| L7 | 119 | L6 and L4 | US-PGPUB; USPAT; EPO; DERWENT | OR | ON | 2005/07/11 08:56 |
| L8 | 41 | L7 and L3 | US-PGPUB; USPAT; EPO; DERWENT | OR | ON | 2005/07/11 08:56 |
| L9 | 29 | (AFx FKHR def-16).clm. | US-PGPUB; USPAT; EPO; DERWENT | OR | ON | 2005/07/11 08:56 |
| L10 | 48 | (glucose insulin) AND (afx OR fkhr OR def-16) | US-PGPUB; USPAT; EPO; DERWENT | SAME | ON | 2005/07/11 08:56 |

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     (FILE 'HOME' ENTERED AT 08:59:05 ON 11 JUL 2005)

     FILE 'MEDLINE, CANCERLIT, AGRICOLA, CAPLUS, SCISEARCH' ENTERED AT
     09:02:32 ON 11 JUL 2005
L1          461 S DAF-16
L2         1536 S AFX OR FKHR
L3        19693 S C. ELEGAN?
L4           21 S L1 (L) L2 (L) L3
L5            7 DUP REM L4 (14 DUPLICATES REMOVED)
L6            0 S L5 AND PY<=1997
              E RUVKUN GARY?/AU

=> d an ti so au ab l5 1-7

L5   ANSWER 1 OF 7     MEDLINE on STN                    DUPLICATE 1
AN   2003538461     MEDLINE
TI   Convergence of peroxisome proliferator-activated receptor gamma and Foxo1
     signaling pathways.
SO   Journal of biological chemistry, (2003 Nov 14) 278 (46) 45485-91.
     Electronic Publication: 2003-09-09.
     Journal code: 2985121R. ISSN: 0021-9258.
AU   Dowell Paul; Otto Tamara C; Adi Saleh; Lane M Daniel
AB   The forkhead factor Foxo1 (or FKHR) was identified in a yeast
     two-hybrid screen as a peroxisome proliferator-activated receptor (PPAR)
     gamma-interacting protein.  Foxo1 antagonized PPARgamma activity and vice
     versa indicating that these transcription factors functionally interact in
     a reciprocal antagonistic manner.  One mechanism by which Foxo1
     antagonizes PPARgamma activity is through disruption of DNA binding as
     Foxo1 inhibited the DNA binding activity of a PPARgamma/retinoid X
     receptor alpha heterodimeric complex.  The Caenorhabditis elegans nuclear
     hormone receptor, DAF-12, interacted with the C. elegans
     forkhead factor, DAF-16, paralleling the interaction
     between PPARgamma and Foxo1. daf-12 and daf-16 have
     been implicated in C. elegans insulin-like signaling
     pathways, and PPARgamma and Foxo1 likewise have been linked to mammalian
     insulin signaling pathways.  These results suggest a convergence of
     PPARgamma and Foxo1 signaling that may play a role in insulin action and
     the insulinomimetic properties of PPARgamma ligands.  A more general
     convergence of nuclear hormone receptor and forkhead factor pathways may
     be important for multiple biological processes and this convergence may be
     evolutionarily conserved.

L5   ANSWER 2 OF 7     MEDLINE on STN                    DUPLICATE 2
AN   2002664265     MEDLINE
TI   Effects of aging and caloric restriction on the gene expression of Foxo1,
     3, and 4 (FKHR, FKHRL1, and AFX) in the rat skeletal muscles.
SO   Microscopy research and technique, (2002 Nov 15) 59 (4) 331-4.
     Journal code: 9203012. ISSN: 1059-910X.
AU   Furuyama Tatsuo; Yamashita Hitoshi; Kitayama Kazuko; Higami Yoshikazu;
     Shimokawa Isao; Mori Nozomu
AB   In C. elegans, insulin-like hormone signal pathway
     plays a significant role in longevity.  In particular, daf-
     16 gene product is indispensable factor for this
     lifespan-extension.  This signal pathway is critical for dauer formation,
     which is a similar state to hibernation in mammals.  We examined the
     expression level of mammalian daf-16 homologues, Foxo
     1,3, and 4 (FKHR, FKHRL1, and AFX) mRNAs in the rat
     skeletal muscles during aging and in 30% caloric restricted of ad libitum
     fed.  The expression level of AFX mRNA was significantly higher
     at 6 and 12 months than at 3 and 26 months, and FKHRL1 expression was
     significantly higher at 6 months than at 3 and 26 months but FKHR
     expression showed no significant change with age.  We observed a
     characteristic expression of AFX and FKHR mRNAs to be
     significantly higher in the second day in caloric restriction by
     every-other-day feeding than in ad libitum fed.  This suggests that
     caloric restriction may increase the expression of FKHR-family
     genes and prevent the aging process in the skeletal muscles.
     Copyright 2002 Wiley-Liss, Inc.
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L5 ANSWER 3 OF 7 MEDLINE on STN DUPLICATE 3
AN 2001308673 MEDLINE
TI Phosphatidylinositol 3-kinase signaling inhibits DAF-16 DNA binding and function via 14-3-3-dependent and 14-3-3-independent pathways.
SO Journal of biological chemistry, (2001 Apr 20) 276 (16) 13402-10. Electronic Publication: 2000-12-20. Journal code: 2985121R. ISSN: 0021-9258.
AU Cahill C M; Tzivion G; Nasrin N; Ogg S; Dore J; Ruvkun G; Alexander-Bridges M
AB In Caenorhabditis elegans, an insulin-like signaling pathway to phosphatidylinositol 3-kinase (PI 3-kinase) and AKT negatively regulates the activity of **DAF-16**, a Forkhead transcription factor. We show that in mammalian cells, **C. elegans DAF-16** is a direct target of AKT and that AKT phosphorylation generates 14-3-3 binding sites and regulates the nuclear/cytoplasmic distribution of **DAF-16** as previously shown for its mammalian homologs **FKHR** and FKHRL1. In vitro, interaction of AKT- phosphorylated **DAF-16** with 14-3-3 prevents **DAF-16** binding to its target site in the insulin-like growth factor binding protein-1 gene, the insulin response element. In HepG2 cells, insulin signaling to PI 3-kinase/AKT inhibits the ability of a GAL4 DNA binding domain/**DAF-16** fusion protein to activate transcription via the insulin-like growth factor binding protein-1-insulin response element, but not the GAL4 DNA binding site, which suggests that insulin inhibits the interaction of **DAF-16** with its cognate DNA site. Elimination of the **DAF-16**/1433 association by mutation of the AKT/14-3-3 sites in **DAF-16**, prevents 14-3-3 inhibition of **DAF-16** DNA binding and insulin inhibition of **DAF -16** function. Similarly, inhibition of the **DAF-16**/14-3-3 association by exposure of cells to the PI 3-kinase inhibitor LY294002, enhances **DAF-16** DNA binding and transcription activity. Surprisingly constitutively nuclear **DAF -16** mutants that lack AKT/14-3-3 binding sites also show enhanced DNA binding and transcription activity in response to LY294002, pointing to a 14-3-3-independent mode of regulation. Thus, our results demonstrate at least two mechanisms, one 14-3-3-dependent and the other 14-3-3-independent, whereby PI 3-kinase signaling regulates **DAF-16** DNA binding and transcription function.

L5 ANSWER 4 OF 7 MEDLINE on STN DUPLICATE 4
AN 2001699838 MEDLINE
TI Regulation of C. elegans DAF-16 and its human ortholog FKHRL1 by the daf-2 insulin-like signaling pathway.
SO Current biology : CB, (2001 Dec 11) 11 (24) 1950-7. Journal code: 9107782. ISSN: 0960-9822.
AU Lee R Y; Hench J; Ruvkun G
AB **C. elegans** insulin-like signaling regulates metabolism, development, and life span. This signaling pathway negatively regulates the activity of the forkhead transcription factor **DAF-16**. **daf-16** encodes multiple isoforms that are expressed in distinct tissue types and are probable orthologs of human FKHRL1, **FKHR**, and **AFX**. We show that human FKHRL1 can partially replace **DAF-16**, proving the orthology. In mammalian cells, insulin and insulin-like growth factor signaling activate AKT/PKB kinase to negatively regulate the nuclear localization of **DAF-16** homologs (reviewed in ). We show that the absence of AKT consensus sites on **DAF-16** is sufficient to cause dauer arrest in daf-2(+) animals, proving that **daf-16** is the major output of insulin signaling in **C. elegans**. **FKHR**, FKRHL1, and **AFX** may similarly be the major outputs of mammalian insulin signaling. daf-2 insulin signaling, via AKT kinases, negatively regulates **DAF-16** by controlling its nuclear localization. Surprisingly, we find that daf-7 TGF-beta signaling also regulates **DAF-16** nuclear localization specifically at the time when the animal makes the commitment between diapause and reproductive development. **daf-16** function is supported by the combined action of two distinct promoter/enhancer elements, whereas the coding sequences of two major

**DAF-16** isoforms are interchangeable. Together, these observations suggest that the combined effects of transcriptional and posttranslational regulation of **daf-16** transduce insulin-like signals in **C. elegans** and perhaps more generally.